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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference FP18112	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416).	
International Application No. PCT/AU2003/000914	International Filing Date (day/month/year) 16 July 2003	Priority Date (day/month/year) 16 July 2002
International Patent Classification (IPC) or national classification and IPC Int. Cl. ⁷ C07D 215/24, 215/26, 215/28, 215/48, A61K 31/47, 31/4709, A61P 25/28		
Applicant PRANA BIOTECHNOLOGY LIMITED et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 26 sheet(s).

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☒ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☒ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 3 February 2004	Date of completion of the report 21 October 2004
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustalia.gov.au Facsimile No. (02) 6285 3929	Authorized Officer STUART BARROW Telephone No. (02) 6283 2284

I. Basis of the report

1. With regard to the elements of the international application:*
- ☐ the international application as originally filed.
- ☒ the description, pages 1-16, 18-20, 22-115, as originally filed,
pages , filed with the demand,
pages 17, 17a-17c, 21, 21a, received on 15 October 2004 with the letter of 13 October 2004
- ☒ the claims, pages , as originally filed,
pages , as amended under Article 19,
pages , filed with the demand,
pages 116-135, received on 15 October 2004 with the letter of 13 October 2004
- ☐ the drawings, pages , as originally filed,
pages , filed with the demand,
pages , received on with the letter of
- ☐ the sequence listing part of the description:
pages , as originally filed
pages , filed with the demand
pages , received on with the letter of
2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language which is:
- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).
3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:
- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished
4. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages
- ☐ the claims, Nos.
- ☐ the drawings, sheets/fig.
5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be nonobvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos: **1-41 (in part)**

because:

☐ the said international application; or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. **1-41 (in part)** are so unclear that no meaningful opinion could be formed (*specify*):

A preliminary search of the claimed subject matter resulted in a very large number of documents likely to anticipate the present claims. The search has therefore been restricted to the exemplified subject matter. The search is not considered to be complete.

Further, the terms "an antioxidant" and "a targeting moiety" are not sufficiently well-defined to allow a complete search.

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claim Nos. **1-41 (in part)**

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

- ☐ restricted the claims.
- ☐ paid additional fees.
- ☐ paid additional fees under protest.
- ☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

- ☐ complied with.
- ☒ not complied with for the following reasons:

The use of compounds with an 8-hydroxyquinoline nucleus in the treatment of neurodegenerative disorders such as Alzheimer's disease is generally known in the art. This is evidenced in part by the extensive provisos characterising the claims. Therefore, the presence of this nucleus can not be considered as a "special technical feature" providing unity to the claims. The claims lack unity *a posteriori*.

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

- ☐ all parts.
- ☒ the parts relating to claims Nos. 1-41 (in part)

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 12-14, 38-41	YES
	Claims 1-11, 15-37	NO
Inventive step (IS)	Claims	YES
	Claims 1-41	NO
Industrial applicability (IA)	Claims 1-41	YES
	Claims	NO

2. Citations and explanations (Rule 70.7)

The following documents were considered when assessing Novelty and Inventive step:

- D1 DE 3932338 A1 (NMI Naturwissenschaftl U Mediz). 11 April 1991
- D2 US 5952346 A (Heitsch et al). 14 September 1999.
- D3 WO 2000/023421 A1 (Idun Pharmaceuticals, Inc). 27 April 2000.
- D4 WO 2000/058344 A1 (Malina). 5 October 2000.
- D5 EP 1074257 A1 (Pfizer Products Inc). 7 February 2002.
- D6 WO 2002/024701 A2 (Pharmacia & Upjohn Company). 28 March 2002.
- D7 WO 2002/024702 A1 (Bristol-Myers Squibb Company). 28 March 2002.
- D8 WO 1999/045907 A2 (The General Hospital Corporation). 16 September 1999.

Novelty

D1 discloses the use of 8-hydroxy quinoline where the hydroxy group is masked with an ester or urethane group in the treatment of Alzheimer's disease. See abstract.

D2 discloses the use of 8-(substituted)benzyloxy quinolines in the treatment of Alzheimer's disease. The group in the R¹ position is considered "substituted alkyl" according to the plain meaning of the term.

D3 discloses in example 34 a compound within the present claims wherein R¹ is "substituted alkyl." The compound is used in the treatment of neurodegenerative diseases.

D4 discloses conjugates of proteins conjugated to Xanthurenic acid used in the treatment of diseases involved in ageing, including neurological conditions. The proteins listed are considered "targetting moieties."

D5 discloses in example 2k a compound within the present claims wherein R¹ is "substituted alkyl." The compound is used in treatment of disorders of the dopamine and serotonin systems.

D6 discloses in examples 125 and 252-263 compounds within the present claims wherein R¹ is "substituted alkyl." The compounds are used in treatment of diseases of the central nervous system.

D7 discloses in example 341 a 5-heterocycle-substituted xanthurenic acid derivative. The compound is used in the treatment of a variety of disease states, including dementia, Alzheimer's disease and short term memory loss.

D8 discloses the use of clioquinol, alone or in use with other agents, as a treatment for Alzheimer's disease. This compound is disclaimed by proviso in the present claims.

Continued on supplemental sheet.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/AU2003/000914

VI. Certain documents cited**1. Certain published documents (Rule 70.10)**

Application No. Patent No.	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
D9 WO 2002/067939 A1	6/9/2002	20/2/2002	27/2/2001
D10 WO 2003/004016 A1	16/1/2003	3/7/2002	5/7/2001
D11 WO 2003/004483 A1	16/1/2003	3/7/2002	5/7/2002
D12 WO 2003/005038 A1	16/1/2003	4/7/2002	5/7/2001
D13 WO 2003/010146 A1	6/2/2003	19/7/2002	20/7/2001
D14 WO 2003/040096 A2	15/5/2003	8/11/2002	8/11/2001
D15 WO 2003/047572 A1	12/6/2003	31/10/2002	4/12/2001

2. Non-written disclosures (Rule 70.9)

Kind of non-written disclosure	Date of non-written disclosure (day/month/year)	Date of written disclosure referring to non-written disclosure (day/month/year)
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VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

The claims are rendered unclear by the excessive use of provisos. The claims define a very broad Markush structure limited by a large number of provisos. The effect of this is to obscure the scope of the claim, such that the addressee can not readily determine what compounds fall within the scope of the claims. The claims should be defined positively, with regard to the common technical features possessed by all members of the claimed group.

The term "isomers" in the claims renders the scope of the claim unclear. Isomers of compounds of formula I are not limited to compounds with the structure of formula I.

The terms "an antioxidant" and "a targeting moiety" in the claims are not sufficiently well-defined and render the scope of the claims unclear.

Claim 9 is not clear. The chemical structure is not consistent with the rest of the claims; for the purpose of this report, this claim has been interpreted as being directed to 8-hydroxy quinoline derivatives.

Proviso (c) in claim 34 is not clear.

Note that claim 2 does not appear to include all relevant provisos, and therefore has a broader scope than claim 1.

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of Box V

With regard to the documents D9-D15 listed in Box VI under "certain documents cited", these are documents published prior to the international filing date but later than the priority date claimed but which would otherwise be considered to be of particular relevance. Each of these documents discloses compounds and uses thereof which anticipate the present claims.

Under the PCT, novelty is considered only in respect of documents published before the priority date. The relevance of a document published after the priority date is dependent upon national law. Such documents are excluded from consideration in preliminary examination, under the PCT Guidelines but have been included here for information.

Inventive Step

D1, D4 and D8 all teach in general the use of xanthurenic acid derivatives in the treatment of disease states including Alzheimer's disease. It would be obvious to one skilled in the art seeking to provide further compounds useful for the treatment of neurological conditions to provide further xanthurenic acid derivatives of similar structure. The subject matter of the present claims can be derived from each of these documents without invention.

Note further that, the above citations notwithstanding, the present claims are distinguished from the prior art by the use of provisos which disclaim known methods. However, this does not constitute an inventive step, as there is no comparative data presented to indicate what advantage, if any, the compounds of the present application have over the prior art. The compounds of the present application are stated to have the same function as the previously known compounds - namely, they are useful in the treatment of neurological conditions. Therefore, for the methods and compounds of Claims 1-41 to be considered inventive, it must be demonstrated that excluding the use of previously known compounds results in some advantage over the prior art.

Industrial Applicability

The presently claimed subject matter is Industrially Applicable according to the practice of the Australian Patent Office. Other jurisdictions may have differing requirements for methods of treatment for a neurological condition.